

# Systematic review and meta-analysis: HuGENet Handbook update

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# Outline

- HuGE reviews
- Systematic review and meta-analysis
- The Handbook
- Developments
- Some questions

# What is a HuGE review?

HuGENet™



A HuGE Review identifies human genetic variations at one or more loci, and describes what is known about the frequency of these variants in different populations, identifies diseases that these variants are associated with and summarizes the magnitude of risks and associated risk factors, and evaluates associated genetic tests. Reviews point to gaps in existing epidemiologic and clinical knowledge, thus stimulating further research in these areas.

We invite authors to write reviews in their area of expertise.

[See Guidelines for Writing a HuGE Review.](#)

**Wang GY, Lu CQ, Zhang RM, Hu XH, Luo ZW. The E-cadherin gene polymorphism 160C->A and cancer risk: A HuGE review and meta-analysis of 26 case-control studies. *Am J Epidemiol.* 2008 Jan 1;167(1):7-14. Epub 2007 Oct 29**

# HuGE reviews

- Originally proposed 1998
  - (Khoury & Dorman, *AJE* 1998)
- More specific guidance for content
  - (*AJE* 2000)
- 2001 expert panel workshop led to recommendations in reporting
  - (Little et al, *AJE* 2002)
- New formats for reviews
  - (Little et al, *AJE* 2003)
- Revised guidance
  - (HuGENet web site 2005)
- 2004 methods workshop led to **HuGE Review Handbook**
  - (Little and Higgins, HuGENet web site, 2006)

# HuGE reviews

- Four types of review were suggested in 2005:
  - Full review
  - Association review
  - Prevalence review
  - Mini-review
- Handbook concentrates on **association reviews**
  - systematic review of gene-disease association studies

# Characteristics of the systematic review process

- Pre-specification of objectives and criteria for including studies
- Comprehensive, systematic search for studies
- Reproducible methods, and duplication of tasks prone to human error
- Appraisal of included studies (including assessment of risk of bias)
- Synthesis of findings (e.g. using meta-analysis)
- Presentation of results in relation to initial objectives

# Data sources for meta-analysis

## Approach

Literature-based systematic review

Literature-based systematic review and liaison with investigators

Consortium-based meta-analysis of existing data

Consortium-based meta-analysis with prospective genotyping

## Some advantages and disadvantages

*Advantages:* low resource requirements

*Disadvantages:* prone to serious bias due to selective availability of data

*Advantages:* relatively low resource requirements

*Disadvantages:* may be prone to bias due to selective availability of data

*Advantages:* data not subject to selective availability; potential to harmonize data

*Disadvantages:* data may be incomplete; inclusion in consortium may be related to findings

*Advantages:* complete data; availability of data unrelated to findings; ability to harmonize methods

*Disadvantages:* genotyping costs

# The HuGE Review Handbook

- A 59-page document describing how systematic reviews of association between genes and disease might be conducted

## The HuGENet™ HuGE Review Handbook, version 1.0

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and HuGE Net Executive Group (Molly Bray, Marta Gwinn, Julian Higgins, John Ioannidis, Muin Khoury, Julian Little, Teri Manolio, Ron Zimmern)



# Key points from the Handbook

1. Encourage **consortia** of primary research investigators as the most reliable approach for performing combined analyses or meta-analyses (based on individual participant data);
2. Adopt methods to minimize human error in literature-based reviews, such as **duplicating selection of studies and data extraction**;
3. Comprehensive (yet practically realistic) searches for eligible studies, considering **sources beyond MEDLINE**;
4. Consider in more detail the **potential for bias** in individual studies and in the total body of available evidence;
5. Encourage the quantitative synthesis of results from multiple studies (**meta-analysis**) where appropriate;
6. Encourage the incorporation of intermediate phenotypes (such as molecular markers) so that '**Mendelian randomization**' can be exploited to examine the causal effects of such phenotypes

# Is the Handbook used?

- Handbook was published on the web in January 2006

20 HuGE reviews published since mid-2006

3 cite the Handbook for review methods

- Gilbody et al (York/Bristol, UK)
- Sanderson et al (Cambridge, UK)
- Wang et al (Shanghai, China)

2 cite the Handbook in the Discussion (within-study bias; reporting bias)

- Smith et al (Oxford, UK)
- Kellen et al (GSEC)

15 don't cite the Handbook at all

# Developments

- Updating to the era of genome-wide association studies
  - guidance on identifying studies; collecting data; deciding on variants to study
- Discussion of use of Mendelian randomization
  - draft text received
- More discussion of meta-analysis
  - collaborative project to develop tutorial and software (Cosetta Minelli, Julian Higgins, John Thompson, Georgia Salanti)

# Some questions

- How do we ensure the Handbook is regularly updated?
  - by the most appropriate people?
- Should we maintain the Handbook?
  - Do people need it or want it?
- Should HuGE reviews be encouraged to follow systematic review methods?
  - or should meta-analyses be encouraged only by consortia of primary investigators
  - or are automated methods a better use of time?
- Should we pursue HuGE reviews?
  - What role of a review of just one association?